

CLAIMS:

1. A mutated adenoviral fiber protein wherein at least one amino acid in the CD loop of a wild-type fiber protein of an adenovirus from subgroup C, D, or E, or the long wild-type fiber of an adenovirus from subgroup F, has been mutated to reduce or substantially 5 eliminate the ability of said fiber protein to bind to the coxsackievirus-adenovirus receptor (CAR).
2. The mutated adenoviral fiber protein of claim 1, wherein said mutation substantially eliminates the ability of said protein to bind to said CAR.
3. The mutated adenoviral fiber protein of claim 2, wherein said fiber protein is an 10 adenovirus serotype 5 fiber protein.
4. The mutated adenoviral fiber protein of claim 3, wherein said fiber protein contains at least one mutation at amino acid positions 441 and 442 of the wild-type fiber protein.
5. The mutated adenoviral fiber protein of claim 4, wherein said fiber protein further comprises a mutation at one or more of the following amino acid positions of the wild- 15 type fiber protein: 408, 409, 460, 509, 510, 538, and 539.
6. The mutated adenoviral fiber protein of claim 4, wherein said fiber protein further comprises at least one mutation at amino acid positions 408 and 409 of the wild-type fiber protein.
7. A mutated adenovirus serotype 5 fiber protein wherein said fiber protein comprises a 20 mutation at one or more of the following amino acid positions of the wild-type fiber protein: 460, 509, 510, 538, and 539, wherein said mutation reduces or substantially eliminates the ability of said fiber protein to bind to CAR.
8. A polynucleotide encoding the protein of claim 1.
9. A polynucleotide encoding the protein of claim 3.
- 25 10. A polynucleotide encoding the protein of claim 4.
11. A polynucleotide encoding the protein of claim 5.
12. A polynucleotide encoding the protein of claim 7.
13. An adenoviral particle comprising the fiber protein of claim 1.
14. An adenoviral particle comprising the fiber protein of claim 3.
- 30 15. An adenoviral particle comprising the fiber protein of claim 4.
16. An adenoviral particle comprising the fiber protein of claim 5.
17. An adenoviral particle comprising the fiber protein of claim 7.
18. The adenoviral particle of claim 13 further comprising a targeting ligand included in a capsid protein of said particle.

19. The adenoviral particles of claim 18 wherein said capsid protein is the mutated adenoviral fiber protein.

20. The adenoviral particle of claim 19 further comprising at least one heterologous polynucleotide.

5 21. The adenoviral particle of any one of claims 14-17 further comprising a targeting ligand included in a capsid protein of said particle.

22. The adenoviral particle of claim 21 wherein said capsid protein is the mutated adenoviral fiber protein.

10 23. The adenoviral particle of claim 22 further comprising at least one heterologous polynucleotide.

24. An adenovirus packaging cell comprising the polynucleotide of claim 8.

25. A method of making the adenoviral particle of claim 13, comprising the steps of:
transferring the adenovirus genome to be packaged in said particle into the packaging cell of claim 24;

15 culturing said packaging cell; and
recovering an adenoviral particle produced by said cell.

26. A method of making the adenoviral particle of claim 18 comprising the steps of:
transferring the adenovirus genome to be packaged in said particle into a cell having adenovirus polynucleotides that provide proteins necessary for the replication, maturation, and packaging of said genome;

20 culturing said cell under conditions permitting the production of said particle; and
recovering an adenoviral particle produced by said cell.

27. A method of expressing a heterologous polynucleotide in a cell comprising infecting said cell with the adenoviral particle of claim 20.

25 28. The method of claim 27, wherein said cell is a mammalian cell.

29. The method of claim 28, wherein said mammalian cell is a primate cell.

30. The method of claim 29, wherein said primate cell is a human cell.

31. A composition comprising the adenoviral particle of claim 18 in a pharmaceutically acceptable carrier.

30 32. A composition comprising the adenoviral particle of claim 20 in a pharmaceutically acceptable carrier.

33. A mutated adenovirus serotype 5 fiber protein wherein said fiber protein contains mutations at amino acid positions 408 and 409 of the wild-type fiber protein.

34. The mutated fiber protein of claim 33, wherein said protein contains deletions at amino acid positions 408 and 409 of the wild-type fiber protein.

35. The mutated fiber protein of claim 33, wherein said protein contains amino acid substitutions at amino acid positions 408 and 409 of the wild-type fiber protein.

5 36. The mutated fiber protein of claim 35, wherein glutamic acid is substituted for serine at position 408 and alanine is substituted for proline at position 409 (SEQ ID NO: 4).

37. A polynucleotide encoding the protein of claims 33-36.

38. An adenoviral particle comprising the fiber protein of claims 33-36.

39. The adenoviral particle of claim 38, further comprising a targeting ligand included in a 10 capsid protein of said particle.

40. The adenoviral particle of claim 39, further comprising at least one heterologous polynucleotide.

41. The adenoviral particle of claim 38, wherein at least one of the penton proteins of said particle has been modified to delete the RGD sequence.

15 42. An adenovirus packaging cell comprising the polynucleotide of claim 37.

43. A method of making the adenoviral particle of claim 38, comprising the steps of:
transferring the adenovirus genome to be packaged in said particle into the packaging cell of claim 42;
culturing said packaging cell; and
recovering an adenoviral particle produced by said cell.

20 44. A method of making the adenoviral particle of claim 38, comprising the steps of:
transferring the adenovirus genome to be packaged in said particle into a cell having adenovirus polynucleotides that provide proteins necessary for the replication, maturation, and packaging of said genome;
culturing said cell under conditions permitting the production of said particle; and
recovering an adenoviral particle produced by said cell.

25 45. A method of expressing a heterologous polynucleotide in a cell comprising infecting said cell with the adenoviral particle of claim 40.

46. The method of claim 45, wherein said cell is a mammalian cell.

30 47. The method of claim 45, wherein said cell is a primate cell.

48. The method of claim 45, wherein said cell is a human cell.

49. A composition comprising the adenoviral particle of claim 40 in a pharmaceutically acceptable carrier.

50. A method of enhancing adenoviral-mediated gene transfer to and expression in hepatocytes comprising the steps of administering adenoviral particles of claim 40 to said hepatocytes.

51. A method of enhancing adenoviral-mediated gene transfer to and expression in hepatocytes comprising the steps of:

5 preparing an adenovirus particle comprising a mutated adenovirus serotype 5 fiber protein, wherein glutamic acid is substituted for serine at amino acid position 408 and alanine is substituted for proline at amino acid position 409, and further comprising a heterologous gene; and infecting hepatocytes with said adenovirus particle.

10 52. A method of expressing a protein in a mammal comprising the step of administering the adenoviral particle of claim 20 or claim 40 to said mammal, wherein said particle transduces a cell in said mammal and said heterologous polynucleotide expresses said protein in said cell.

53. The method of claim 52, wherein said mammal is a primate.

15 54. The method of claim 53, wherein said primate is a human.

55. A method of expressing a protein in the liver of a mammal comprising administering a sufficient amount of the adenoviral particles of claim 40 for said particles to transduce cells in the liver of said mammal.

56. The method of claim 55, wherein said amount comprises approximately 1 particle per 20 kilogram of body weight to approximately 10^{13} particles per kilogram of body weight.

57. The method of claim 55, wherein said amount comprises approximately 10^4 particles per kilogram of body weight to approximately 10^{12} particles per kilogram of body weight.

58. The method of claim 55, wherein said amount comprises approximately 10^8 particles per kilogram of body weight to approximately 10^{11} particles per kilogram of body weight.

25 59. An adenoviral vector comprising the polynucleotide of any one of claims 8-12.

60. An adenoviral vector comprising the polynucleotide of claim 37.

61. The adenoviral particle of claims 13, 18, 20, 38, 39, 40, or 41, wherein said adenoviral particle is a replication conditional adenovirus.

62. The adenoviral particle of claim 61, wherein said adenovirus is an oncolytic adenovirus.